Apparently NOCl and N_2O_3 were searched since the office action indicates claims directed to NOCl and N_2O_3 would be allowable except for the double patenting rejection. Thus, the search was extended to N_2O_3. The search was also extended to H_2S since this is the subject of the 112 rejection. However, the search apparently was not extended to the rest of the genus. This is improper. If the elected species is not found in the prior art, the entire genus must be searched. A search of the rest of the genus, is therefore requested.

We turn now to the rejections.

Claims 1-5 are rejected for obviousness type double patenting over U.S. Patent No. 6,314,956. A terminal disclaimer is enclosed. The fee under 37 CFR 1.20(d), that is $55 on a small entity basis, is enclosed (Check No. 17604); if any further fee is necessary for the terminal disclaimer to be effective, please charge the same to Deposit Account No. 10-1213. Reconsideration of the rejection is requested.

Claims 1-3 and 6-9 are rejected under 35 U.S.C. 112, first paragraph on the basis that sufficient disclosure on how to use H_2S is not provided in the application as filed in view of Embase abstract 2000083448, Chemical Abstracts 115:56107 and Medline Abstract 92296647. Reconsideration is requested in view of the positions below.

Firstly, consider that a regimen as to how to use for H_2S, is clearly stated in the application as filed at page 12, lines 8-12. Thus, the rejection has to be based on the utility for Claim 6 not being credible. Presumably, the office action is citing the three abstracts to make a *prima facie* case that no credible utility has been properly established for H_2S and to cause applicant to bear the burden of rebutting this.

It is submitted that the three abstracts do not indicate any deficiency in the protocol for H_2S explicitly recited in the application as filed or discredit the utility of H_2S for treatment of asthma or for any other disorder that Claim 1 addresses.

Medline 92296647 states that changes in pulmonary function caused by H_2S exposure (apparently in air) suggests that asthmatics are at risk. EMBASE 2000083446 states that some asthmatics may demonstrate signs of bronchial constriction as a result of 2 ppm hydrogen sulfide (apparently in air) for 30 minutes. These disclosure are submitted to be problematical and thus not pertinent.

Chemical Abstracts 115:56107 discloses that a minor proportion of asthmatics experience changes indicating bronchial obstruction after being exposed to 2 ppm of hydrogen sulfide for 30 minutes in a exposure chamber (which would have to otherwise contain air). This regimen differs from that of page 12, lines 8-12 and Example X in that the H_2S is administered in a chamber containing air and not in nitrogen and thus should not cast doubt on applicant's disclosed regimen.

In any event, even if the three abstracts indicate that a minor proportion of asthmatics experience airway obstruction on treatment with applicant's disclosed regimen (which it is submitted, they do not), this does not negate the enablement provided by and operativeness of applicant's disclosed regimen since most drugs effect difficulties in some proportion of subjects to which they are administered and yet are recognized as being important for treatment. One skilled in the art would know that in those cases where difficulties ensue, the treatment is discontinued.

Consider what the PDR says about Celebrex®:

> A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more

> severe hepatic reaction while on therapy with CELEBREX. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), CELEBREX should be discontinued.

This scenario is also the case for treatments causing lung obstruction. In this regard, consider that acetylcysteine is an FDA approved drug for use as a mucolytic for cystic fibrosis patients despite the fact that in some patients, mucolytics may aggravate airway obstruction. In those cases, the offending regimen is discontinued and another regimen implemented. See The Merck Manual 17th Edition, pages 513 and 514, copy enclosed.

Obviously, one skilled in the art would discontinue H_2S treatment in those some cases where there would be a problem. This is submitted not to be grounds for disparaging the invention or negating patentability.

Examination of the whole of generic Claim 1 and allowance of all claims are requested.

Respectfully submitted,

JONES, TULLAR & COOPER, P.C.

By: _____
Eric S. Spector
Reg. No. 22,495

JONES, TULLAR & COOPER, P.C.
P.O. Box 2266 Eads Station
Arlington, Virginia 22202
703-415-1500

Case Duke File 1661 CIP

Date: December 27, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

The paragraph beginning at line 4 of page 15 has been amended as follows:

A 25-year-old white male presents to the emergency room with an asthmatic exacerbation. The forced expiratory volume in 1 second (FEV1) is 0.8 liters per minute. Following the standard bronchodilator regimen, the FEV1 increases to 1.5 liters per minute but breathing is still labored. GSNO levels in the airway lining are depleted. The patient is begun on H_2S gas at 10 ppm in nitrogen and over the following day the FEV1 increases to 1.8 liters per minute. Ethyl [nitrate] nitrite is then started at 10 ppm in nitrogen and the FEV1 increases to 2 liters per minute.--

IN THE CLAIMS:

New Claims 10-12 have been added as follows:

10. The method of Claim 6 where the H_2S is administered at a dosage of 0.1 to 100 ppm in nitrogen.

11. The method of Claim 10 where the H_2S is administered after administration by inhalation of nitric oxide.

12. The method of Claim 1 where the agent does not comprise H_2S.

SEVENTEENTH EDITION

THE MERCK MANUAL OF DIAGNOSIS AND THERAPY

Editors
MARK H. BEERS, M.D., and ROBERT BERKOW, M.D.

Senior Assistant Editors
ROBERT M. BOGIN, M.D., and
ANDREW J. FLETCHER, M.B., B.Chir.

Published by MERCK RESEARCH LABORATORIES
Division of MERCK & CO., INC.
Whitehouse Station, N.J. 1999

antitussive may reduce the input of stimuli by acting as a mild analgesic or anesthetic on the respiratory mucosa, by modifying the output and viscosity of the respiratory tract fluid, or by relaxing the smooth muscle of the bronchi in the presence of bronchospasm. On the efferent side, an antitussive may make secretions easier to cough up by increasing the efficiency of the cough mechanism. Peripherally acting agents are grouped as demulcents, local anesthetics, and humidifying aerosols and steam inhalations.

Demulcents are useful for coughs originating above the larynx. They form a protective coating over the irritated pharyngeal mucosa. They are usually given as syrups or lozenges and include acacia, licorice, glycerin, honey, and wild cherry syrups.

Local anesthetics (eg, lidocaine, benzocaine, hexylcaine hydrochloride, and tetracaine) are used to inhibit the cough reflex under special circumstances (eg, before bronchoscopy or bronchography). Benzonatate (100 mg po tid), a congener of tetracaine, is a local anesthetic; its antitussive effect may be due to a combination of local anesthesia, depression of pulmonary stretch receptors, and nonspecific central depression.

Humidifying aerosols and steam inhalations exert an antitussive effect by acting as a demulcent and by decreasing the viscosity of bronchial secretions. Inhaling water as an aerosol or as steam, with or without medicaments (sodium chloride, compound benzoin tincture, eucalyptol), is the most common method of humidification. The efficacy of added medicaments has not been clearly proved.

Expectorants: These drugs are intended to help expel bronchial secretions from the respiratory tract by decreasing their viscosity, thus facilitating removal, and by increasing the amount of respiratory tract fluid, thus exerting a demulcent action on the mucosal lining. Most expectorants increase secretions through reflex irritation of the bronchial mucosa. Some, like the iodides, also act directly on the bronchial secretory cells and are excreted into the respiratory tract.

The use of expectorants is highly controversial. No objective experimental data show that any of the available expectorants decreases sputum viscosity or eases expectoration. Data may be lacking partly because of inadequate technology for obtaining such evidence. Thus, the use and choice of expectorants are often based on tradition and the widespread clinical impression that they are effective in some circumstances.

Adequate hydration is the single most important measure that can be taken to encourage expectoration. If it is unsuccessful, using an expectorant in addition may produce the desired result.

Iodides are used to liquefy tenacious bronchial secretions (eg, in late stages of bronchitis, bronchiectasis, and asthma). A saturated solution of potassium iodide is the least expensive, most commonly used preparation. The initial dose is 0.5 mL po qid, in a glass of water, juice, or milk after meals and at bedtime, which is increased gradually to 1 to 4 mL qid. To be effective, iodides must be taken in doses approaching intolerance. Their usefulness is limited by low patient acceptance because they have an unpleasant taste and because side effects (eg, acneiform skin eruptions, coryza, erythema of face and chest, painful swelling of the salivary glands) are common. The side effects are reversible and subside when the drug is stopped. Iodinated glycerol is better tolerated than potassium iodide solution but is probably less effective. The usual oral dosage is 60 mg as tablets or elixir qid; *it should be avoided in patients sensitive to iodide.* Prolonged use of iodides or iodinated glycerol can lead to hypothyroidism.

Syrup of ipecac 0.5 mL po qid (NOTE: This is much less than the emetic dose) can be used as an expectorant in patients sensitive to iodides. It is useful for relieving laryngeal spasm in children with croup and often clears thick, tenacious mucus from the bronchi.

Guaifenesin (100 to 200 mg po q 2 to 4 h) is the most commonly used expectorant in OTC cough remedies. It has no serious adverse effects, but there is no clear evidence of its efficacy.

Many other traditional expectorants (eg, ammonium chloride, terpin hydrate, creosote, squill) are found in numerous OTC cough remedies. Their efficacy is doubtful, particularly in the dosages of most preparations.

Less commonly used drugs: Mucolytics (eg, acetylcysteine) have free sulfhydryl groups that open mucoprotein disulfide bonds, reducing the viscosity of mucus. As a

rule, their usefulness is restricted to a few special instances such as liquefying thick, tenacious, mucopurulent secretions (eg, in chronic bronchitis and cystic fibrosis). Acetylcysteine is given as a 10 to 20% solution by nebulization or instillation. In some patients, mucolytics may aggravate airway obstruction by causing bronchospasm. If this occurs, these patients may inhale a nebulized sympathomimetic bronchodilator or take a formulation containing acetylcysteine (10%) and isoproterenol (0.05%) before taking the mucolytic.

Proteolytic enzymes (eg, pancreatic dornase) are useful only when grossly purulent sputum is a major problem. They seem to offer no advantage over mucolytics. Local irritation of the buccal and pharyngeal mucosa and allergic reactions commonly follow repeated doses. Dornase alfa, the new highly purified recombinant human deoxyribonuclease I (rhDNase), seems likely to become important in the treatment of cystic fibrosis, although its place has not been defined.

Antihistamines have little or no use in treating cough. Their drying action on the respiratory mucosa may be helpful in the early congestive phase of acute coryza but may be deleterious, especially to patients with a nonproductive cough resulting from retained viscous airway secretions. They may also be beneficial in chronic cough due to postnasal drip associated with allergic sinusitis.

Bronchodilators (eg, ephedrine and theophylline) may be useful if cough is complicated by bronchospasm. Atropine is *undesirable* because it thickens bronchial secretions. The anticholinergic drug ipratropium bromide can often ameliorate an irritating type of cough and does not adversely affect mucus secretions. Inhaled corticosteroids have become a mainstay in the treatment of cough in asthma.

Drug combinations: Many prescription and OTC cough remedies contain two or more drugs, usually in a syrup. They may include a centrally acting antitussive, an antihistamine, an expectorant, and a decongestant. Bronchodilators and antipyretics are also often present. These combinations are aimed at treating the many symptoms of an acute URI and should not be used to manage cough alone. Some antitussive combinations are appropriate for cough (eg, a centrally acting antitussive, such as dextromethorphan, and a peripherally acting demulcent syrup for cough originating above the larynx). However, the components of some combinations (eg, expectorants and antihistamines) have opposing effects on respiratory tract secretions, and many combinations contain suboptimal or ineffective concentrations of potentially useful ingredients.

Choice of drug therapy: As a rule, when cough alone is a major problem, using a full dose of a single drug aimed at a specific component of the cough reflex is preferred. For simple suppression of a nonproductive cough, dextromethorphan is preferred, but codeine is also useful. The more potent narcotic antitussives should be reserved for cases in which analgesic and sedative effects are required and the cause is likely to be temporary. To increase bronchial secretion and liquefy viscous bronchial fluid, adequate hydration (by drinking water or inhaling steam) is used; a saturated solution of potassium iodide or syrup of ipecac given orally may be tried if hydration alone is unsuccessful. To relieve cough originating in the pharyngeal region, demulcent syrups or lozenges, combined if necessary with dextromethorphan, are used. For bronchoconstriction associated with cough, bronchodilators, possibly combined with expectorants, are advised; inhaled corticosteroids may be effective in some cases.

DYSPNEA

An unpleasant sensation of difficulty in breathing.

Dyspnea is a symptom, not a sign, and is one of several sensations a patient may describe. A healthy person notes the increased ventilation required during exercise but does not interpret it as being particularly unpleasant unless extreme. Unpleasant or worrisome awareness that a small amount of exercise leads to a disproportionately large increase in ventilation is a common type of dyspnea, usually described as breathlessness or shortness of breath on exertion. At high altitude, a healthy person notes a similar disproportionately large increase in ventilation resulting from exertion and finds it limiting but usually not otherwise unpleasant.

Other sensations include awareness of increased muscular effort required to expand the chest during inspiration or to expel air from the lungs, sensations of fatigue in the